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Mindfulness-oriented recovery enhancement in opioid use disorder: Extended emotional regulation and neural effects and immediate effects of guided meditation in a pilot sample

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ABSTRACT

Objective: Mindfulness-Oriented Recovery Enhancement (MORE) is an efficacious intervention to aid recovery from substance use disorder. This study in a pilot sample of individuals in treatment for opioid use disorder (OUD) characterizes longer-term changes after the MORE intervention and immediate effects of a brief MORE guided meditation session.

Design: Twelve female participants in residential treatment for OUD completed an 8-week MORE intervention. Participants completed two sessions: one before and one after the 8-week MORE intervention. Each session included an emotional regulation questionnaire outside an MRI scanner first and then a 10-minute guided MORE meditation inside the scanner during which functional magnetic resonance imaging (fMRI) data were collected. Emotional regulation was measured after 8-weeks of MORE intervention. In addition, functional connectivity (i. e. correlated fMRI signal) between regions in a hypothesized affect regulation network was measured during the meditation state to assess change in brain network function due to 8-weeks of MORE. For each 10-min guided meditation, we also assessed their mood and opioid craving.

Results: Nine participants completed all measurements. Participants' emotional regulation difficulty significantly decreased after 8-weeks of MORE intervention. Furthermore, after 8-weeks of MORE, there was significantly increased connectivity between left ventromedial prefrontal cortex and left amygdala and between left ventrolateral prefrontal cortex and left nucleus accumbens captured during a meditation state. In both sessions, positive mood significantly increased after 10-min of guided mediation, however opioid craving was not significantly influenced.

Conclusions: This pilot study characterizes potential benefits of 8-week MORE intervention in improving emotional regulation difficulty and brain function. A 10-min guided MORE meditation may immediately improve mood, with potential to reduce acute stress- or cue-provoked craving. These results warrant future studies with larger sample size.

According to CDC (2015), the rate of opioid use disorder (OUD) among women in the U.S. is increasing (up 100% in women versus 50% in men for heroin use from 1999-2010) which is one critical factor driving the national surge in opioid related overdoses. Women,

compared to men, report higher opioid craving, trauma, and negative affect and show a greater inability to control their drug urges at treatment entry.¹ As a gold standard, medications for opioid use disorder (MOUD) have demonstrated short-term efficacy by limiting biological

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changes associated with acute withdrawal, via receptor occupancy. However, issues pertaining to longer-term adherence as well as relapse to other illicit drugs remains a major obstacle.² Deficits in regulating negative affect and in responding to natural rewards are identified as potential underlying target processes.³ While MOUD including buprenorphine (BUP) increases receptor occupancy, it may not fully engage the core regulatory and affective processing circuits underpinning adaptive control over negative emotion, and hence be less able to restrain opioid craving and compulsive opioid seeking. Moreover, women have been found to have lower rates of treatment progress and completion for both MOUD and therapy-alone treatment.⁴

Thus, there is a critical need for adjunctive therapies capable of improving long-term clinical outcomes in women with OUD. Mindfulness-Oriented Recovery Enhancement (MORE), a behavioral intervention, has demonstrated efficacy across multiple randomized clinical trials in reducing opioid misuse, craving, and pain in individuals with co-occurring OUD and pain.^{5,6} MORE integrates training in mindfulness, cognitive reappraisal skills, and savoring of natural rewards into an 8-week group therapy designed to remediate hedonic dysregulation in brain reward systems.⁶ The intervention is based on dual-process theories of addiction tailored specifically to target the hedonic dysregulation that undergirds OUD.^{7,8} However, potential neural changes in pathways hypothesized to underlie emotion regulation and craving are not well studied with respect to MORE. To date, only two studies have examined the impact of the MORE on brain function among people with chronic opioid use; both studies used encephalography (EEG) and found that the MORE meditation elicited increases in frontal midline theta EEG activity that were associated with decreased opioid use and misuse.⁶ To date, no studies have used functional magnetic resonance imaging (fMRI) to examine the effects of MORE among people with OUD. This research area is important to study as there are no other behavioral treatments for OUD in women that have shown to regulate these mechanisms and the results have implications for reducing opioid use and relapse in women with OUD.

In this study, we examined effects of MORE in an initial proof-of-concept study among in-patient treatment seeking women with OUD. The volunteers completed 8-weeks of MORE bookended by two assessments of emotion regulation difficulty and functional connectivity of brain regions using fMRI. Functional connectivity was measured while participants were in a meditation state to allow a focused assessment of changes that occur in brain network communication after participants are trained to effectively use meditation as a tool for recovery. Thus, the functional connectivity measure was repeated before and after the 8-week MORE intervention to allow analysis of changes. We hypothesized that (1) after 8-weeks of MORE intervention, difficulty with emotional regulation will decrease and functional connectivity will increase between regions hypothesized to underlie emotion regulation (prefrontal cortex [PFC] and amygdala) and control over craving (PFC and nucleus accumbens),⁹ and (2) guided MORE meditation will be associated with immediate increase in positive mood and decrease in opioid craving.

Methods

Participants

Twelve female participants with moderate-to-severe OUD and in the first three months of residential treatment with MOUD (i.e., buprenorphine) were enrolled in the study at the first assessment. Two participants left the residential treatment before the second assessment. One participant was unable to enter the scanner for the second assessment due to change in MR contraindications and completed the procedures in a behavioral testing room. This participant is included in the emotional regulation report analyses (N=10, mean age = 38.60 years, range 29-54 years; mean years of education = 12.5 years, range 7-15 years) but excluded from neuroimaging analysis (N = 9, mean age = 38.67 years,

range 29-54 years; mean years of education = 12.5 years, range 7-15 years). Of 10 participants, 8 were White (1 Hispanic) and 2 were Black. The majority of participants' last year household income fell below \$20,000, only 3 reported household income above \$20,000. Along with MOUD, other treatment modalities included Motivational Interviewing, Dialectical Behavioral Therapy, Eye Movement Desensitization & Reprocessing, and Contingency Management based on their needs and comfort. Participants also attended weekly Narcotics Anonymous (NA) meetings. All participants completed informed consent and procedures were approved by the Rutgers University Institutional Review Board.

Procedures

Participants completed the first assessment, the 8-week MORE intervention during residential treatment, and then the second assessment (Fig. 1). The assessments were identical and conducted at Rutgers University Brain Imaging Center. First, participants completed demographic and emotion regulation questionnaires,¹⁰ and then they entered the MR environment for scanning. Participants listened to a 10-minute guided MORE meditation³ in the scanner while viewing a picture of an outdoor garden, and blood oxygen level dependent images were recorded to measure functional connectivity during the meditation (see supplement for full MR acquisition description).

The 10-minute guided MORE meditation involves mindfully focusing attention on sensations of breathing, while acknowledging and accepting mind wandering. The meditation then invites participants to de-center from thoughts and emotions into the perspective of an objective observer or witness. The meditation culminates with instructions to focus on the space of awareness in which mental contents arise. The participants listened to a recorded voice guiding them through the meditation. The same recording was played in both sessions.

Weekly 2-hour MORE sessions involved training in mindfulness, reappraisal, and savoring skills.³ Each session began with the guided MORE meditation practice (described above), followed by psychoeducation, and sessions culminated with an experiential exercise (meditation practice that varies from week to week). MORE-sessions were delivered by a clinician trained in MORE intervention. Intervention adherence was monitored by the clinician.

This manuscript focuses on (a) changes in emotional regulation difficulty, and (b) changes in neural functional connectivity captured during a meditation state from pre- to post-8-week MORE intervention. Additionally, the manuscript also examines the effects of a guided MORE meditation on immediate positive mood and opioid craving.

Emotional regulation analysis

Emotional regulation ability was measured by the Difficulties in Emotional Regulation Scale (DERS¹⁰) completed at both pre- and post-8-week MORE sessions (see Fig. 1). Total scores and all subscale scores were evaluated using paired t-tests (pre- versus post-MORE) to examine changes in emotional regulation abilities following MORE intervention (effect size reported as within-subjects Cohen's d).

Neuroimaging analysis

Functional neuroimaging data from the 10-minute guided MORE meditation were analyzed similarly to a typical resting state functional connectivity study, allowing examination of pre- to post-8-week MORE change in functional connection strength (correlation) between brain regions during the meditation. Preprocessing of images collected during each 10-minute meditation was implemented with *fMRIPrep* 20.2.6¹¹ followed by the eXtensible Connectivity Pipeline (XCP^{12,13}), which implemented alignment, slice timing interpolation, normalization, and motion scrubbing. Connectivity matrices were calculated for each scan as Pearson correlation coefficients between nodes of interest defined

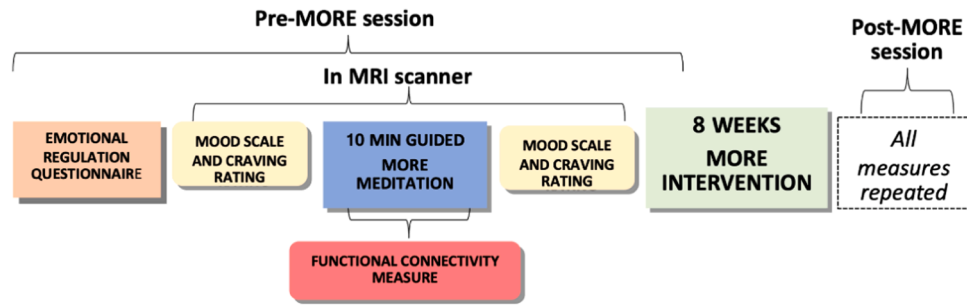


Fig. 1. Timeline of procedures. Primary measures were collected in two sessions: one session before MORE intervention, then measures were repeated in an identical session conducted after the 8-week MORE intervention. Mood and craving assessments were repeated twice in each session to measure changes linked to the 10-minute guided meditation.

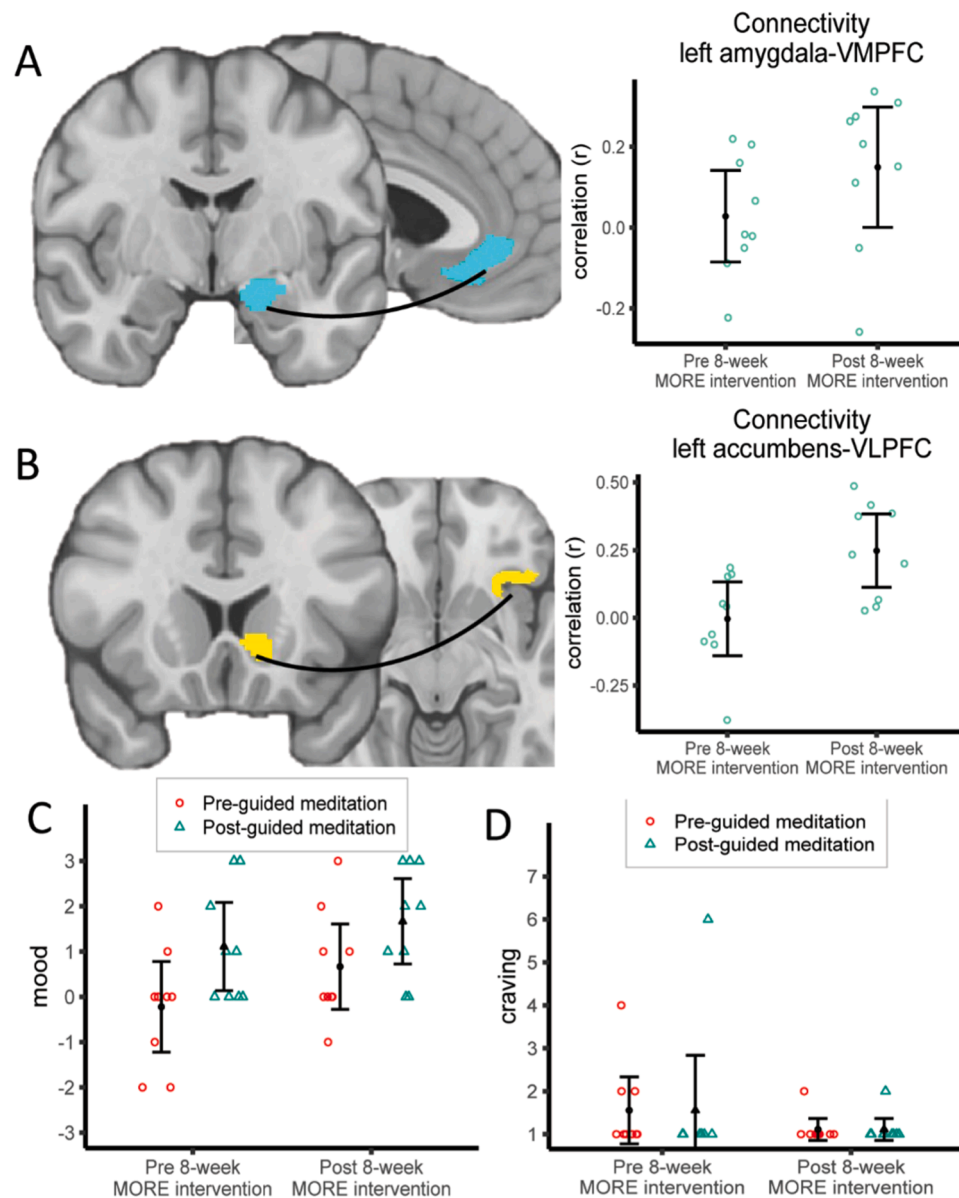


Fig. 2. Neural functional connectivity and self-report results. (A and B) Subcortical-prefrontal connectivity was measured by inter-region signal correlation during the 10-minute guided meditation, yielding a measure of functional connectivity pre-MORE intervention and another measure 8 weeks later post-MORE intervention. Functional connectivity change from pre- to post-MORE intervention was observed in (A) left amygdala-VMPFC and (B) left nucleus accumbens-VLPFC. Brain images depict the regions of interest. All plots show mean (black points) and individual (colored shapes) correlations between regions. Error bars show 95% confidence interval for the sample mean. Before and after each 10-minute guided meditation (repeated in sessions pre- and post-MORE intervention) participants reported on their (C) mood and (D) opioid craving.

from cortical¹⁴ and subcortical¹⁵ atlases: dorsolateral prefrontal (DLPFC), ventrolateral prefrontal (VLPFC), posterior ventromedial prefrontal (VMPFC), lateral amygdala, medial amygdala, and nucleus accumbens core (all bilateral, yielding 12 nodes). These correlation coefficients described the correlation strength of 10-minute signal time series (600 time points) from each pair of brain regions (i.e., signal time series correlation over the 10-minute meditation). These nodes were selected for their hypothesized roles in affective regulation and were defined as the atlas region containing prefrontal, amygdala, or nucleus accumbens peaks from a meta-analytic map of regions associated with the term “emotion regulation” (NeuroQuery⁹). Changes in connectivity (pre- versus post-MORE) between all connections were examined by paired t-tests conducted on r-to-z transformed correlation coefficients. Uncorrected p-values are reported due to the small sample (66 connections in total were tested).

Mood and craving analysis

Mood and opioid craving were measured by 7-point ratings (mood: -3[extremely negative] to 3[extremely positive], craving: 1[none at all] to 7[a great deal]) before and after the 10-minute guided meditation in each session. Ratings were analyzed by 2 (pre/post-meditation) X 2 (pre/post-MORE) ANOVA (effect size reported as partial η^2).

Results

MORE-intervention adherence: Of 10 participants, 9 participants completed all 8 MORE intervention sessions, and 1 participant completed 7 sessions.

Emotional regulation: Participants improved (lower difficulty score) on DERS total regulation difficulty following 8-week MORE intervention, $t(9) = 3.10$, $p = 0.013$, $d = .979$. This change was most pronounced in the impulse control difficulty subscale, $t(9) = 2.97$, $p = 0.016$, $d = .940$ and lack of emotional awareness subscale, $t(9) = 3.68$, $p = 0.016$, $d = 1.64$.

Neural functional connectivity during 10-minute guided MORE meditation: Among the connections examined where pre- to post-8-week MORE intervention changes were hypothesized, VMPFC-amygdala and VLPFC-nucleus accumbens showed significant increases. The connection between left VMPFC and left medial amygdala showed a significant increase from pre-MORE intervention ($r = .028$) to post-MORE intervention ($r = .149$, post-MORE – pre-MORE: $t(8) = 2.784$, $p = .024$, $d = .984$) (see Fig. 2A). Additionally, the connection between left VLPFC and left nucleus accumbens showed a significant increase (pre-MORE $r = -.004$; post-MORE $r = .248$; post-MORE – pre-MORE: $t(8) = 2.676$, $p = .028$, $d = .946$) (see Fig. 2B); see Tables S1-S2 for information on connections between all nodes (i.e., regions).

Mood and Craving: Mood increased immediately after 10-min guided meditation at both pre- and post-MORE intervention, main effect $F(1,9) = 7.503$, $p = 0.023$, partial $\eta^2 = .45$ (Fig. 2C). MORE intervention (and pre-/post-meditation interaction) did not significantly influence mood ratings (main effect: $F(1,9) = 2.919$, $p = 0.122$; interaction: $F(1,9) = 0.156$, $p = 0.703$). Opioid craving ratings were not significantly influenced by pre-/post-meditation, by pre-/post-MORE intervention, or by the interaction (Fig. 2D), though 7 participants were at the lowest craving rating possible in the pre-MORE session (before meditation) and 9 were at the lowest level in the post-MORE session (before and after meditation). Craving ratings were at the lowest for most, but decreased after 8-week MORE intervention for those not at lowest.

Discussion

In this pilot study we examined the effects of 8-week MORE intervention on changes in emotional regulation difficulty and neural functional connectivity among women in residential treatment, with OUD,

and maintained on MOUD. This study is the first to evaluate changes in fMRI functional connectivity after an 8-week MORE intervention in women with OUD on MOUD. Results demonstrated that emotional regulation improved following 8-week MORE intervention in opioid-using women on MOUD, consistent with our hypothesis. More specifically, study participants' impulse control difficulty and lack of emotional awareness improved significantly, as indicated by their subscale scores pre- and post-MORE intervention. Our imaging results support these behavioral findings wherein the 8-week MORE intervention resulted in significantly increased functional connectivity between (1) prefrontal regulatory/emotional regions (left VMPFC and left medial amygdala) and (2) prefrontal regulatory/reward processing regions (left VLPFC and left nucleus accumbens) captured during a meditative state, consistent with our hypotheses. Further research is needed to characterize how changes in these prefrontal-subcortical connections may relate to changes in emotional processing or craving regulation. We speculate that improved connectivity between prefrontal and amygdala regions perhaps support MORE's conceptual framework⁶ in terms of its efficacy in enhancing positive emotional processing. Furthermore, increased connectivity between prefrontal and nucleus accumbens regions may support MORE-induced improved reward regulation that may promote less opioid craving and relapse in women with OUD. Indeed, prior studies have shown that MORE increases responsiveness to natural healthy rewards which are in turn associated with decreased craving.⁵

In addition, we examined the immediate effects of a guided MORE meditation on mood and craving. Consistent with hypothesized immediate affective benefits of guided MORE meditation, mood increased from before to after the 10-minute meditation at both pre- and post-8-week MORE intervention. This brief meditation-related increase was not altered by the 8-week MORE intervention. Opioid craving was low (near the floor of the scale) pre-MORE after receiving MOUD treatment for at least 2 months, which impaired power to detect potential decreases in craving after guided meditation at pre- and post-8-week MORE assessments. Although the mood improvement is over a brief time period, momentary affect is an important factor for understanding drug relapse/recovery and the findings support prior evidence that MORE intervention effectively reduces opioid craving, negative affect and emotional distress in people who use opioids and have chronic pain.⁶ Regarding transient affective states that are important for understanding relapse/recovery from OUD⁶ the findings further show that a guided MORE meditation even without prior MORE intervention can show immediate mood increase that may prevent relapse in the face of acute stress- or cue-provoked craving.

This was a pilot study, and thus the design did not include a control group nor a large sample. Additionally, since MORE was delivered alongside other behavioral therapies such as Motivational Interviewing and Dialectical Behavioral Therapy, this pilot study is unable to isolate the independent effects of MORE on the outcomes. Despite these shortcomings, the results show evidence that an 8-week MORE intervention may improve emotional dysregulation and create long-term neuroplasticity in the regulatory and emotional/reward neurocircuitry that have implications for reduced craving and relapse for women with OUD on MOUD. In addition, we show evidence that mood momentarily improves after a 10-minute guided MORE meditation and therefore may have implications for reducing drug relapse. In the future, large RCTs are warranted to examine the efficacy and mechanisms of MORE in women with OUD and other substance use disorders.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.explore.2023.11.001](https://doi.org/10.1016/j.explore.2023.11.001).

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